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(21) International Application Number: PCT/IT99/00331 (22) International Filing Date: 19 October 1999 (19.10.99) (30) Priority Data: B098A000596 21 October 1998 (21.10.98) IT (71) Applicant (for all designated States except US): SIGMA-TAU HEALTHSCIENCE S.P.A. [IT/IT]; Via Treviso, 4, I-00040 Pomezia (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): FEHER, Janos [HU/IT]; Via Roma, 69, I-02034 Montopoli in Sabina (IT). SEARS, Grazia [IT/IT]; Via Evelino Tosarello, 9, I-45030 S. Maria Maddalena (IT). (74) Agents: CAVATTONI, Fabio et al.; Cavattoni - Raimondi, Viale dei Parioli, 160, I-00197 Roma (IT).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>	
(54) Title: UBIQUINONE-CONTAINING COMPOSITION SUITABLE FOR PROMOTING ENHANCED INTRAMITOCHONDRIAL TRANSPORTATION OF UBIQUINONES AND METHODS OF USING SAME (57) Abstract A composition is disclosed which comprises as characterizing active ingredients a lipid-soluble benzoquinone, e.g. Coenzyme Q ₁₀ and at least one omega-3 polyunsaturated fatty acid selected from the group consisting of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and linoleic acid (LNA), for the prevention and/or treatment of mitochondriopathies.		

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Ubiquinone-containing composition suitable for promoting enhanced intramitochondrial transportation of ubiquinones and methods of using same.

The present invention relates to a pharmaceutical/nutritional composition for supporting and/or providing therapy to individuals at risk and/or under treatment for dysfunctions of energy metabolism, and specifically, for mitochondrial diseases.

More specifically, the present invention relates to a composition comprising (a) an amount of a lipid-soluble benzoquinone selected from the group consisting of ubiquinone (Coenzyme Q₁₀, CoQ₁₀), its reduced form, ubiquinol-10 (CoQ₁₀H₂) or mixtures thereof, effective for performing a therapeutical and/or preventive and/or nutritional activity, and (b) at least a further component suitable for stimulating and enhancing the intramitochondrial transportation of component (a), the resulting composition being potentially effective for the prevention and/or treatment of mitochondriopathies.

Accordingly the composition may take the form and exert the action of a dietary or nutritional supplement or of an actual medicine, depending upon the support or preventive action, or the strictly therapeutic action, which the composition is intended to exert in relation to the particular individuals it is to be used in. Depending on the actual circumstances, the composition of the present invention need not or, alternatively, should be taken under the supervision of an attending physician.

In the publication by the United Mitochondrial Disease Foundation, "About Mitochondria and Disease" (<http://biochemgen.ucsd.edu/umdf/AboutMitoDisease.htm>), which is incorporated herein by reference, the following definition of what a mitochondrial disease is, and what the triggering, sub-cellular causes are, is given:

"The mitochondria produce adenosine triphosphate (ATP), the body's mobile energy source. When mutations occur which affect the mitochondria, the vital supply of ATP is disrupted, less and less energy is generated within the cell. When this process is repeated on a large scale throughout the body, whole systems begin to fail, and the life of the person in whom this is happening can be compromised, changed or even ended. The cells that require the most energy, like the brain, heart and skeletal muscles, are the most vulnerable".

This reference also provides a detailed list and description of mitochondrial diseases, which encompasses, *inter alia*, Co-enzyme Q₁₀ deficiency; Complex III deficiency (Ubiquinone - cytochrome c oxidoreductase deficiency) whose symptoms include pigmentary retinopathy; Complex IV deficiency/COX deficiency (cytochrome c oxidase deficiency) whose symptoms include optic atrophy and ophthalmoplegia; CPEO (Chronic Progressive External Ophthalmoplegia Syndrome) whose symptoms include visual myopathy and retinis pigmentosa; ARMD (Age-Related Macular Degeneration); NARP (Neuropathy, Ataxia and Retinis pigmentosa) and many others.

Since CoQ₁₀ is indispensable to cellular bioenergetics, its deficiency may bring about a host of pathologies.

Indeed, CoQ₁₀ is known to play an essential role as an electron (redox) carrier in the mitochondrial electron transport chain of the cell. However, it also protects membrane phospholipids and those in LDL from peroxidation as well as protects and/or regenerates vitamin E. CoQ₁₀ is synthesized in the body from precursors of cholesterol synthesis and therefore is not classed as a vitamin. However, the ability to synthesize CoQ₁₀ decreases with age and there may be an increasing dependence on food to supply the nutrient. The most abundant sources are fresh unprocessed foods, particularly meats, fish, nuts and seed oils. The average daily intake of CoQ₁₀ is approximately

2 mg.

Ubiquinol-10 or CoQ₁₀H₂, the reduced form of CoQ₁₀, plays a second role as a potent lipid-soluble antioxidant and its activity at physiological concentrations in the lipid components of cells has recently been shown.

CoQ₁₀'s antioxidative, electron transport, and membrane-stabilizing properties have widely been investigated aiming at prevention of and/or treatment of various cardiovascular diseases, including prevention of cellular damage during reperfusion, angina pectoris, hypertension, myocardial ischemia, and congestive heart failure.

In patients with mitochondrial encephalomyopathy, CoQ₁₀ treatment increases mitochondrial functions and exercise performance, and reduces the acidosis associated with exercise. This finding is consistent with CoQ₁₀ participation in electron transport and mitochondrial membranes, and in the biological oxidation of cellular fuels for energy generation.

CoQ₁₀ deficiency was also reported to be associated with viral infections, and supplementation of CoQ₁₀ in acquired immune deficiency syndrome (AIDS) patients resulted in enhanced macrophage activity and increased serum level of IgG. CoQ₁₀ treatment has been reported to provide some benefits in cancer patients, and enhanced hematopoietic activity in malnourished children. All the evidence suggests that CoQ₁₀ may play essential roles in maintaining and promoting health, under normal and abnormal conditions.

It has become more and more apparent that individuals at risk and/or under treatment for mitochondriopathies are in need of increased supplementation of ubiquinones with respect to the normal intake of these substances through the diet, since particularly CoQ₁₀ deficiency may cause the onset, precipitate or aggravate the symptoms of a serious mitochondriopathy.

Many efforts have been made over the last decade in order to find formulations that would increase the bioavailability of CoQ₁₀ or anyhow enhance its efficacy at the cellular organelle sites of action. For instance, M. Weis et al in "Bioavailability of four oral Coenzyme Q₁₀ formulations in healthy volunteers (Molec. Aspects Med. Vol. 15 [supplement] pps 273-s 280, 1994) report on a four-way randomised cross-over trial wherein the bioavailability of four different CoQ₁₀ formulations was compared. The study results suggest that a soy bean oil suspension of CoQ₁₀ (Bioquinon®, 100 mg CoQ₁₀ with 400 mg of soy bean oil in soft gelatine capsules) exhibits the highest bioavailability.

However, in spite of all these efforts, no satisfactory formulations able to provide a therapeutical or preventive effective concentration of ubiquinons and particularly of CoQ₁₀ at their intracellular sites of action, have been developed to-date.

Polyunsaturated fatty acids (PUFA) are subdivided in classes based on the location of the first double bond counting from the methyl end of the fatty acid molecule: ω -3 (or n-3) fatty acids have their first double bond between the third and fourth carbon atoms, and the ω -6 (or n-6) fatty acids have their first double bond between the sixth and seventh carbon atoms. Particularly importante are the ω -3 fatty acids and, specifically, linolenic acid (18:3 ω 3) (LNA), eicosapentaenoic acid (20:5 ω 3) (EPA), and docosahexaenoic acid (22:6 ω 3) (DHA), wherein the first number (before the colon) gives the number of carbon atoms in the molecule and the second gives the number of double bonds.

In the last two decades, epidemiologic studies, clinical investigations and animal experiments have expanded our knowledge of the properties of dietary fatty acids in health and disease, growth and development. As a recent result of these investigations, the focus is on the ratio of ω -6/ ω -3 fatty acids in the diet; the essentiality of ω -3 fatty acids and their metabolic effect in the prevention and treatment of chronic diseases. These biological and functional effects of ω -3 fatty acid exert profound beneficial metabolic changes in coronary heart

disease, hypertension, non-insulin-dependent diabetes mellitus, inflammatory and autoimmune disorders, and possibly cancer. For a detailed account on the sources, metabolism, biological and functional effects and dietary aspects of ω -3 fatty acids see e.g. "Functional Food" edited by Israel Goldberg, Chapman & Hall (1994), Chapter 16: "Fatty Acids" by Artemis P. Simopoulos, pp 355-392, which is incorporated herein by reference.

We have now found that a combination composition comprising in admixture:

(a) a lipid soluble benzoquinone selected from the group consisting of Coenzyme Q₁₀, (CoQ₁₀), its reduced form, ubiquinol-10 (CoQ₁₀H₂) or mixtures thereof, in an amount effective for performing a therapeutical and/or preventive and/or nutritional activity in a human need thereof; and

(b) at least one omega-3 polyunsaturated fatty acid or an ester thereof,

is able to enhance the pharmacological/nutritional effects of CoQ₁₀ and/or CoQ₁₀H₂.

Although it is neither intended nor necessary to rely on any theoretical interpretation to account for the aforesaid enhanced effects, it is apparent that, most likely, they are due to the omega-3 polyunsaturated acid acting as bioactive vehicles for CoQ₁₀ and/or CoQ₁₀H₂ and boosters of the intramitochondrial transportation thereof to their sites of action.

The omega-3 polyunsaturated acid is selected from the group consisting of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), linolenic acid (LNA) or mixtures thereof. EPA and DHA or mixtures thereof are particularly preferred. Preferred esters of LNA, EPA or DHA are the triglycerides and the ethyl ester.

The composition may also comprise saturated, monounsaturated, omega-6 and omega-9 fatty acids or mixtures thereof. Examples of such

acids are palmitic acid (16:0), oleic acid (18:1 ω 9), linoleic acid (18:2 ω 6), and arachidonic acid (20:4 ω 6) or mixture thereof. If one or more of these non omega-3 fatty acids are present, the amount of the aforesaid omega-3 fatty acids, particularly EPA and/or DHA, preferably exceeds 65% and is lower than 95% by weight of the overall mixture of omega-3 fatty acids.

The weight ratio DHA:EPA in the composition ranges from 1:1 to 1:20, preferably from 1:1 to 1:5.

The weight ratio (b):(a) in the composition ranges from 1:20 to 1:50.

The composition of the present invention may further comprise α -tocopherol (vitamin E) as component (c). Preferably, the weight ratio (b):(c) in the composition ranges from 1:20 to 1:50. We have found that the aforesaid omega-3 fatty acids act as bioactive vehicles towards Vitamin E as well, i.e. they enhance the pharmacological effects of Vitamin E.

The efficacy of the compositions according to the present invention towards many forms of mitochondriopathies and the ability of the same compositions to enhance the intramitochondrial transportation of CoQ₁₀ was shown in clinical trials. As an instance of the successful treatment of a mitochondriopathy, a study on patients affected by photophobia and ARMD is reported hereinbelow.

The following retinal model for assessing mitochondriopathy was used.

As known, reactive oxygen species (ROS) may be generated at least at three sites in the retina:

- in the photoreceptor cell during light stimulation.
- in the retinal pigmented epithelium (RPE), which phagocitizes photoreceptor discs during normal turnover and light stimulation.
- in the neuroretina at the synaptosomes.

In each of these three sites, mitochondria are the common source and target of ROS.

We found that in the normal retina, mitochondrial membranes of the photoreceptor cells have significantly different molecular structure than those of the outer segment discs. The mitochondrial membranes are more basophilic, and they contain more unsaturated lipids than the disc membranes of the outer segments. Further, *in vitro* studies of normal human photoreceptors cells showed, that the behaviour of mitochondrial and disc membranes is different when they are exposed to oxido-reductive stress. The same oxidative stress which resulted in reversible alteration of the disc membranes, caused irreversible damage of the mitochondrial membranes. However, the exposure to strong electron donor substances (chlorpromazines) slightly altered the structure of mitochondrial membranes, but it disrupted the disc membranes in dose dependent manner. These findings suggested that mitochondrial membranes are more sensible to oxidative, while disc membranes are more sensible to reductive influences.

Via electron microscopic studied on diseased human retinas, we showed that mitochondrial damage is a typical alteration in age-related macular degeneration (ARMD), myopic retinal dystrophies (MRD) and in retinitis pigmentosa (RP). Mitochondrial alterations included loss of the cristae, accumulation of intramitochondrial lipid droplets, swollen of the mitochondria, and decrease in number of them were observed in diseased RPE and photoreceptors cells. Pigment epithelial cells were predominantly affected in ARMD and MRD, while in RP both photoreceptor and pigmented epithelial cells were seriously altered.

These findings suggested that the retina is a suitable model for assessing mitochondriopathy.

We performed open, controlled studies of the various compositions of CoQ₁₀ and alpha tocopherol with or without the addiction of omega-3

fatty acids. In each series of healthy volunteers and photophobia patients the treatment was applied for one month, while in the series of ARMD patients it was for three months. To evaluate visual function before and after treatment, as well as after one month of "wash-out" macular photostress test was applied.

Macular Photostress Test: 60 seconds bright light illumination to one eye (the follow eye was covered) by standardized slit lamp (full aperture and maximum intensity of a Haag-Streit slit lamp). Contrast sensitivity was tested by Maffei decimal chart before and after the illumination and the recovery time was measured (i.e. measured the time when the eye was able to read the same figure, as before the photostress). This function of the retina depends on the metabolic support to light stimulation-regeneration, thus a very suitable method for evaluate mitochondrial functions (Wu, G., Weiter, J.J., Santos, S., Ginsburg, L., Villalobos, R.: The macular photostress test in diabetic retinopathy and age-related macular degeneration. Arch. Ophthalmol., 108, 1556-58 (1990).

Blood levels of total, HDL, and LDL cholesterol and triglicerid levels were evalutated before, after three months of treatment, and after one month "wash-out" in the ARMD group.

a) Healthy volunteers

12 healthy volunteers were enrolled in this clinical trial (6 male, 6 female, aged 24-37 years, mean body weight 66,5 kg).

1st group: treated with 50 mg CoQ₁₀ granulated + 70mg vitamin E/day

2nd group: treated with 100 mg CoQ₁₀ granulated + 70mg vitamin E/day

3rd group: treated with 30 mg CoQ₁₀ in soy bean oil + 30 mg vitamin E/day

4th group: treated with 30 mg CoQ₁₀ in omega-3 (>65% conc.) + 30 mg Vitamin E/day

Results

- healthy volunteers react very poorly to these treatments;
- pharmacological effect of 50 mg CoQ₁₀ granulated + vitamin E was insignificant;
- lipid addition improved dose-efficacy relation of CoQ₁₀ + vitamin E (100 mg. CoQ₁₀ granulated were equivalent 30 mg of CoQ₁₀ dissolved in soy bean oil);
- highly concentrated PUFA was the most effective treatment.

b) Photophobia patients

16 patients suffered from photophobia were enrolled in this trial (11 female, 5 male, aged 23-44 years, mean body weight 63,4 kg).

1st group: treated with 100 mg CoQ₁₀ granulated + 70 mg vitamin E/day

2nd group: treated with 30 mg CoQ₁₀ in soy bean oil + 30 mg vitamin E/day

3rd group: treated with 30 mg CoQ₁₀ in fish oil (>30% conc.) + 30 mg vitamin E/day

4th group: treated with 30 mg CoQ₁₀ in omega-3 (>65% conc.) + 30 mg Vitamin E/day

Results

The pharmacological effect of CoQ₁₀ + vitamin E was approximately double in cases of photophobia than in healthy volunteers.

- omega-3 enhances intensity and duration of the pharmacological effects of CoQ₁₀ + vitamin E;

- higher concentration of omega-3 was showed better effects than lower concentration: the differences were 50% after one month of treatment, and approximately 30% after one month of "wash-out".

c) Retinal dystrophy patients

43 patients affected by early age-related macular degeneration (visual acuity better than 20/40) were involved in these studies (23 female, 20 male, aged between 55-66 years, mean body weight 66,8 kg).

1st group: treated with lutein + zeaxantin + vitamin E (a commercially available product)

2nd group: treated with 1.000 mg omega-3 (>65%) only

3rd group: treated with fish oil + 30 CoQ₁₀ + 30 mg vitamin E/day

4th group: treated with omega-3 (>65%) + 30 mg CoQ₁₀ + 30 mg Vitamin E/day

Results

There were no significant differences between the groups treated with a commercially available dietary supplement (containing lutein, zeaxantin and vitamin E) and omega-3 (>65%) alone.

- CoQ₁₀ + vitamin E in highly concentrated omega-3 was more effective than fish oil + CoQ₁₀ + vitamin E, after 3 months (50%) and after one month of wash-out (30%);
- highly concentrated (>65%) PUFA showed synergistics pharmacological effects with CoQ₁₀ and vitamin E, superior than those of low concentration PUFA or saturated lipids;
- highly concentrated (>65%) PUFA administration showed lowering of the plasma triglyceride levels and improved the ratio of total/HDL cholesterol, which was not observed in fish oil (30% omega-3) treated cases. In contrary, in 3 of the 12 cases, increase of total cholesterol and/or triglycerid levels were observed.

Table I
Healthy volunteers

	Treatment	Wash-out
50 mg CoQ ₁₀ gran + 70 mg vit. E	0,9%	0,5%
100 mg CoQ ₁₀ gran + 70 mg vit. E	4,3%	0,9%
30 mg CoQ ₁₀ + 30 mg vit. E + soy bean oil	5,7%	0,6%
30 mg CoQ ₁₀ + 30 mg vit. E + 858 mg omega-3	7,2%	2,4%

Table II
Photophobia patients

	Treatment	Wash-out
100 mg CoQ ₁₀ gran + 70 mg vit. E	6,4%	-2,3%
30 mg CoQ ₁₀ + 30 mg vit. E + soy bean oil	7,3%	-1,2%
30 mg CoQ ₁₀ + 30 mg vit. E + 1.000 mg fish oil	9,4%	3,1%
30 mg CoQ ₁₀ + 30 mg vit. E + 858 mg omega-3	18,1%	9,4%

Table III
Age-Related Macular Degeneration

	Treatment	Wash-out
Lutein - Zeaxantin - mg vit. E	6,2%	-0,8%
1.000 mg omega-3	7,0%	1,0%
30 mg CoQ ₁₀ + 30 mg vit. E + 1.000 mg fish oil	7,8%	2,1%
30 mg CoQ ₁₀ + 30 mg vit. E + 858 mg omega-3	15,1%	7,3%

Conclusions

These pharmacological studies showed that CoQ₁₀ + vitamin E in a vehicle of highly concentrated polyunsaturated fatty acids improved retinal function, primarily the regeneration of photoreceptor cells in normal conditions and in diseases states.

The most likely cellular target of these substances is the mitochondria of photoreceptor cells. The longer duration of visual improvement, a particularly important pharmacological effect, indicates that the composition of the present invention achieves a higher intracellular concentration of CoQ₁₀ and/or higher affinity of this substance to the target organelles than those accomplished via the usual enterally administrable CoQ₁₀-containing formulations at present commercially available.

The following examples of compositions are offered by way of illustration only and not by way of limitation.

Example 1: 700 mg (*) soft gelatine capsule

Eicosapentaenoic acid (EPA)	148.72 mg
Docosahexaenoic acid (DHA)	105.82 mg
Linolenic acid (LNA)	31.46 mg
Coenzyme Q ₁₀	10.00 mg
Proteins	137.00 mg
Carbohydrates	63.00 mg

Example 2: 1,420 mg (*) soft gelatine capsule

Eicosapentaenoic acid (EPA)	340 mg
Docosahexaenoic acid (DHA)	240 mg
Linolenic acid (LNA)	70 mg
Coenzyme Q ₁₀	20 mg
Vitamin E	20 mg
Proteins	300 mg
Carbohydrates	150 mg

(*) The balance to 700 mg (or 1,420 mg, respectively) is accounted for considering that the omega-3 fatty acids are present as triglycerides.

CLAIMS

1. A combination composition comprising in admixture the following components:
 - (a) a lipid-soluble benzoquinone selected from the group consisting of Coenzyme Q₁₀ (CoQ₁₀), its reduced form, ubiquinol-10 (CoQ₁₀H₂) or mixtures thereof, in an amount effective for performing a therapeutical and/or preventive and/or nutritional activity in a human in need thereof; and
 - (b) at least one omega-3 polyunsaturated fatty acid or an ester thereof.
2. The composition of claim 1, wherein the omega-3 polyunsaturated fatty acid is selected from the group consisting of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and linolenic acid (LNA) or mixtures thereof.
3. The composition of claims 1-2, wherein the ester of eicosapentaenoic, docosahexaenoic or linolenic acid is selected from the triglycerides or the ethyl ester.
4. The composition of claims 1-3 which further comprises a non omega-3 fatty acid selected from a saturated, monosaturated, omega-6 or omega-9 fatty acid or a mixture thereof.
5. The composition of claim 4 wherein the non omega-3 fatty acid is selected from the group consisting of palmitic acid, oleic acid, linoleic acid, arachidonic acid or mixtures thereof.
6. The composition of claims 4 or 5, wherein the amount of the omega-3 fatty acid exceeds 65% by weight of the overall mixture of omega-3 and non omega-3 fatty acids.

7. The composition of claim 6 wherein the amount of the omega-3 fatty acid is lower than 95% by weight of the overall mixture of omega-3 and non omega-3 fatty acids.
8. The composition of claims 2-7, wherein the weight ratio DHA:EPA ranges from 1:1 to 1:20.
9. The composition of claim 8, wherein the weight ratio DHA:EPA ranges from 1:1 to 1:5.
10. The composition of claims 1-9, wherein the weight ratio (b):(a) ranges from 1:20 to 1:50
11. The composition of claims 1-10, further comprising (c) α -tocopherol (vitamin E).
12. The composition of claim 11, wherein the weight ratio (b):(c) ranges from 1:20 to 1:50.
13. The composition of claims 1-12 which further comprises one or more additives selected from the group consisting of vitamins, mineral salts, antioxidizing agents, aminoacids, polysaccharides and vegetal fibers.
14. The composition of claims 1-13 in solid, semisolid, liquid, semiliquid, powder, granular or liposomic form, and occurring as tablets, capsules, granulates, powders and vials for the oral or parenteral administration.
15. Use of:
 - (a) a lipid-soluble benzoquinone selected from the group consisting of Coenzyme Q₁₀ (CoQ₁₀), its reduced form, ubiquinol-10 (CoQ₁₀H₂) or mixtures thereof, in an amount effective for performing a therapeutical and/or preventive and/or nutritional activity in a human in need thereof, in admixture with

(b) at least one omega-3 polyunsaturated fatty acid or an ester thereof, for preparing a nutritional/pharmaceutical composition for preventing or treating a condition affecting humans in need of an enhanced intramitochondrial transportation of said benzoquinone.

16. The use of claim 15, wherein said condition is a mitochondriopathy.

17. The use of claim 16, wherein the mitochondriopathy is selected from Co-enzyme Q₁₀ deficiency; Complex III deficiency (Ubiquinone - cytochrome c oxidoreductase deficiency); Complex IV deficiency/COX deficiency (cytochrome c oxidase deficiency); CPEO (Chronic Progressive External Ophthalmoplegia Syndrome); ARMD (Age-Related Macular Degeneration) and NARP (Neuropathy, Ataxia and Retinis pigmentosa).

18. The use of claims 15-17, wherein the nutritional/pharmacological composition further comprises Vitamin E.

INTERNATIONAL SEARCH REPORT

Intern. Patent Application No

PCT/IT 99/00331

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/23 A61K31/20 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 895 652 A (V.C.GIAMPAPA) 20 April 1999 (1999-04-20) claim 1 column 1, line 11-21 column 10, line 11-21	1,2,4,5, 11,13-18
X	WO 98 33476 A (G.VOLDEN) 6 August 1998 (1998-08-06) claims 1,8 page 7, line 9-17	1,2,11, 13,15, 17,18
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No.

PCT/IT 99/00331

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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